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Experimental Psychoses

WHICH MIMIC Schizophrenia*

Doctor Fabing seizes upon the recent discovery that lysergic acid diethylamide will produce a psychosis that mimics schizophrenia. He then relates, in a most interesting manner, the results of a search through "anthropological lore" wherein many instances are found suggesting that primitive peoples in various parts of the world have found and used "hallucinogenic" or "psychotomimetic" substances. The author stresses the fact that most of these substances are of plant-origin and are related to indoles. Exceptions, however, are noted.

—EDITOR

THERE is a fascinating word in the English language called *serendipity*. It has to do with making a chance observation and not ignoring it, with following through when somebody stumbles upon something, and of pursuing it to a profitable end. This kind of fortuitous observation, or serendipity, occurred about a decade ago, and has opened up a whole new exciting chapter in the study of schizophrenia.

In recent years we have heard a great deal about the importance of psychiatric illness as a public health problem, and about a series of new treatment methods, ranging from deep insulin therapy to electroshock therapy, to prefrontal leukotomy, to the new tranquilizing drugs and to psychoanalysis. If we are honest with ourselves, none of these things has thrown much light on etiology. They are all empirical therapeutic methods. As doctors we can not afford to turn up our noses at empiricism. We have always been willing to use something if it seemed to work. Foxglove tea was used for shortness of breath long before we knew about digitalis and myocardial failure. Jesuit bark was used for recurring fever long before we knew about quinine and malaria, and we continue to be opportunists in therapy wherever our knowledge is unsure. It is our constant hope, however, to get at the cause of disease processes, and to build a rational therapy on a solid foundation of etiology.

We do not know the etiology of the most cruel of mental diseases, schizophrenia, but you may be interested in some recent efforts

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in this direction, many of which stem from a chance observation, or serendipity. A research chemist named Hoffmann, working in the Sandoz Laboratories in Basle, Switzerland, sucked up something in his mouth from a pipette. He had been working with ergot extracts, and was making esters of one of its components, lysergic acid. In less than an hour he was muddled, confused and hallucinated. Frightened, he left the laboratory and got on his bicycle. He pedaled what seemed like five thousand miles to his home which was in reality a short distance away, but he had lost time and space perception. He called his doctor who managed to get him to gulp down all the milk in the house, but his psychotic state persisted until he fell into a fitful sleep late that night. Four days later he returned to his laboratory, looked over his notebooks and decided that he had swallowed the dextro-rotatory diethylamide of lysergic acid. Gingerly he measured out a very minute amount of the material and took another swallow. The psychosis returned, this time worse. He pedaled ten thousand miles home, and again drank all the milk in sight to no avail. Thus, LSD-25 was born. Here was an experimental way of producing a psychosis which had very much the look and feel of schizophrenia. It takes about one-seven-hundred-millionth of a healthy young man's weight of this material to produce a model psychosis of five to ten hours.

The minuteness of the dose and the magic of its effects have been tested and retested all over the world since Hoffman's accident was first reported, in 1947. One would have to be a stick or a stone not to have his imagination completely captivated by the drama of an LSD psychosis. Hoffmann's observation has fired clinicians, chemists, enzymologists and pharmacologists into new activity everywhere. It has caused us to take a new look at old things. A search through anthropological lore discloses that primitive men have used many things throughout history to "look through the doors of percep-

*Read before Annual Convention Nebraska State Medical Association, May 16, 1956.

tion into other-worldly experience," as Aldous Huxley has called it. A whole series of seeds, roots, mushrooms, leaves and other botanical products have been employed to produce visual hallucinations, loss of time and space perception, detachment from the world about us, and states of ecstasy.

These drugs were called "phantastica" by the Germans, and recently they have been labelled as "hallucinogenic or psychotomimetic agents, because they are capable of producing hallucinations and they mimic the psychosis, schizophrenia, in many ways. *Cannabis indica*, or hashish, or marihuana as we know it, derived from the flowering tops of the female hemp plant, is perhaps the oldest of these agents in man's employ. Chinese writings indicate that it was used as early as the 15th century before Christ, and its employment as an hallucinogen is almost world wide.

On this continent one of the most widely used hallucinogenic agents has been peyote, derived from the dried flowers of a small cactus, *Anhalonium lewinii*. The active principle of this plant is mescaline. A large literature on this drug's ability to produce a schizophrenia-like withdrawal into a world of inner experience, detached and split off from the real everyday world of men and affairs, has arisen over the last sixty years. One of the first American investigators of mescaline was Wier Mitchell, the famous Philadelphia neurologist and novelist, in the 1890's. You may study its effects today to the west and south of us among the Peyote Indians of our American Southwest, and in northern Mexico.

South of the Isthmus of Panama, stretching all the way from Haiti to Argentina, another plant derivative has been used for centuries for these purposes. Fra Ramon Pane, who came to America with Columbus on his second voyage, reported the use of *cohoba* among the Indians in A.D. 1496. This ancient narcotic snuff was made by grinding up the seeds of the *Piptadenia peregrina* tree with lime. The resulting powder was snuffed into the nose. Pane wrote of its effects as follows: "It intoxicates them to such an extent that while they are under its influence they know not what they do." It became tribal custom for the women to tie up the Otomaco Indians when they inhaled this snuff in order to keep them from destroying themselves or others during the hours while the drug effect lasted. Recently

it has been determined that the active chemical principle of cohoba is bufotenine, a compound first found in the skin and parotid gland secretions of poisonous toads.

Half-way across the earth from South America, in Eastern Siberia, the Koryaks and other tribes of the Kamchatka peninsula have used for untold centuries a certain species of mushrooms, *Amanita muscaria**, commonly known as fly-agaric, to produce states of ecstasy and visionary experience of almost-schizophrenic type. The first European to describe the practice was von Strahlenberg, in 1730. Prodigious feats of physical strength are reported under its influence. Vanderlip wrote, "Curiously enough, after recovering from one of these debauches, they claim that all the antics performed were by command of the mushroom."

Jochelsen, who travelled among the Koryaks in 1900-01, wrote:

"Fly-agaric produces intoxication, hallucinations, and delirium. Light forms of intoxication are accompanied by a certain degree of animation and some spontaneity of movements. Many shamans, previous to their seances, eat fly-agaric to get into ecstatic states . . . Under strong intoxication the senses become deranged; surrounding objects appear either very large or very small, hallucinations set in, as do spontaneous movements and convulsions. So far as I could observe, attacks of great animation alternate with moments of deep depression. The person intoxicated by fly-agaric sits quietly rocking from side to side, even taking part in conversations with his family. Suddenly his eyes dilate, he begins to gesticulate convulsively, converses with persons whom he imagines he sees, sings, and dances. Then an interval of rest sets in again. However, to keep up the intoxication additional doses of fungi are necessary . . . There is reason to think that the effect of fly-agaric would be stronger were not its alkaloid quickly taken out of the organism with the urine. The Koryak knows this by experience, and the urine of persons intoxicated with fly-agaric is not wasted. The drunkard himself drinks it to prolong his hallucinations, or he offers it to others as a treat."

*This beautiful fungus crowned by a vivid red cap dotted with white spots was depicted by Walt Disney in the "Dance of the Mushrooms" with Tchaikowsky's Nutcracker Suite music in Fantasia.

The drinking of the Siberian mushroom eater's urine during these *amanita* debauches has been noted by many other travellers. It is reported that such urine can be drunk successively by as many as five people, passing in and out of one into the next, so that all of them can gain the hallucinogenic effect from one dose of mushrooms. It would be most revealing to know the chemical composition of the hallucinogen which is passed around in the urine of these tribesmen, but this fact is not known. In 1953, Wieland and Motzel, employing paper chromatographic analysis, determined that this mushroom *Amanita muscaria*, as well as *A. mappa*, and *A. pantherina*, all contained bufotenine, or n-n-dimethyl serotonin, the same chemical found in the cohoba snuff of South America.

Among the Vikings who flourished in Iceland and Scandinavia during the Middle Ages, there was apparently another mushroom-eating practice. The act of *going berserk*, or *Berserksgang*, as they called it, seems to have been due to the eating of the same *Amanita muscaria* mushroom as that used thousands of miles away by nomadic tribes of Siberians. A vivid description of their behavior is given by Schubeler:

"In the old Norwegian historical writings it is mentioned, in many places, that in olden times there was a specific kind of giants who were called *Berserks*, that is, men who at certain times were seized by a wild fury, which, at the moment, doubled their strength and made them insensible to bodily pain, but which also deadened their humanity and reason, and made them like wild animals. This fury, which was called "*Berserksgang*," occurred not only in the heat of battle, but also during laborious work. Men who were thus seized performed things which otherwise seemed impossible for human power. This condition is said to have begun with shivering, chattering of the teeth, and chill in the body, and then the face swelled and changed its color. With this was connected a great hotheadedness, which at last went over into a great rage, under which they howled as wild animals, bit the edge of their shields, and cut down everything they met, without discriminating between friend or foe. When this condition ceased, a great dulling of the mind and feebleness fol-

lowed, which could last for one or several days."

Samuel Lorenzo Oedman wrote of the Berserks, in 1784, as follows:

"On these giants fell sometimes such a fury that they could not control themselves, but killed men or cattle, whatever came in their way and did not take care of itself. While this fury lasted they were afraid of nothing, but when it left them they were so powerless that they did not have half of their strength and were as feeble as if they had just come out of bed from a sickness. This fury lasted about one day."

Oedman saw in this fury followed by a state of exhaustion a paroxysm, and stated, "I am not of the opinion that these ecstasies can be explained as effects of a peculiar temperament or of auto-suggestion because . . . they were not able to keep up their hated arrogance between paroxysms."

He argued further, "Since the vegetable kingdom gives us various means to bring our power of imagination into chaos and to induce the most ferocious excesses of courage, I am inclined to believe that the Berserks had knowledge about such an intoxicating means, and that they made use of it and kept it secret so that their prestige would not be reduced by the general populace's knowledge of the simplicity of the technique." He then reviewed the possible botanical products indigenous to Scandinavia which might have been used in this manner, and decided that "*flugsvamp*," the *Amanita muscaria* mushroom, was the one which solved the riddle of the Berserks. Recently we injected bufotenine into prisoners at the Ohio State Penitentiary who volunteered for the experiment. The drug effect was rapid and relatively transient under intravenous conditions, but it was reminiscent of LSD and mescaline responses.

In addition to these amazing uses of botanical products by man throughout history, one could name harmine, derived from the Turkish plant, *Peganum harmala*; yohimbine from the bark of the yohimbeho tree; ibogaine, an African plant substance, and many others. There are 13 "phantastica" which are said to be used by the Mexican Indians alone.

There are probably two questions which arise in your minds about this catalogue of

oddities of human behavior. The first is: why do they do it? The second is: how does this weird assortment of things relate to the clinical disease, schizophrenia? The answer to the first question—why did, and why do men do these things—is something of a guess. Aldous Huxley's recent small book, "Heaven and Hell" puts forth the challenging theory that the visionary experiences un-

HALLUCINOGENS OF VEGETABLE ORIGIN

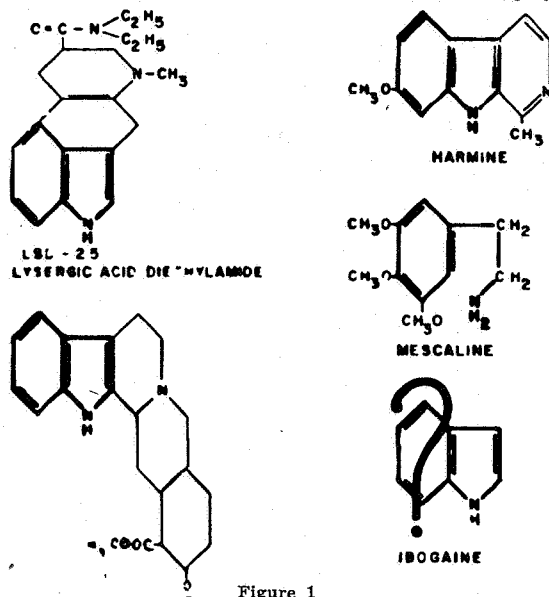


Figure 1

der these drugs have given men a glimpse into what they think Heaven is like—and perhaps Hell, too, if they get an upsetting experience from these drugs.

As for the possible relationship of these drug effects to clinical schizophrenia, nothing can be said with finality at this time, but some suggestive leads seem to emerge. LSD, bufotenine, yohimbine, ibogaine and harmine are all indoles. Mescaline probably cyclizes into an indole in the body. Porphobilinogen, the probable causative agent of acute intermittent porphyria, is somewhat close to an indole in structure. These compounds are important in biology and in human biochemistry. All indoles are not hallucinogenic for man by any means, but a reasonably large number seem to be so. The indoles are chemical changelings, and seem to be capable of rapid structural alteration. The thought arises that abnormal indoles may arise in the human body by metabolic error, and that these indoles may poison our brains and thus make us schizophrenic. At the moment this is only a thought, but as the chemists keep delving into the evidence, the thought becomes a more respectable one.

I should like to add two more pieces of "indole evidence" to the pathogenesis of schizophrenia. W. K. Sherwood, a marine biochemist, while working in his laboratory with tryptophane, one of the amino-acids which is a normal protein constituent, noted that when he manipulated the compound in acid-ether extraction, fumes arose from his laboratory benches which rendered him "schizophrenic" for periods of more than three or four days on numerous occasions before he realized what was happening to him. The offending substance is not fully identified chemically as yet, but it is an indole. The fumes have caused him to have headache, a feeling of strangeness and remoteness, and an inability to communicate with others. It has made him feel like two people, himself and the "Outside Talker." His thought processes became jumbled and he sat and stared at his laboratory work. Others noted the onset of his symptoms before he did.

The second piece of evidence deals with adrenaline. When adrenaline sits around in a bottle for a long time it turns pink.

HALLUCINOGENS OF ANIMAL ORIGIN

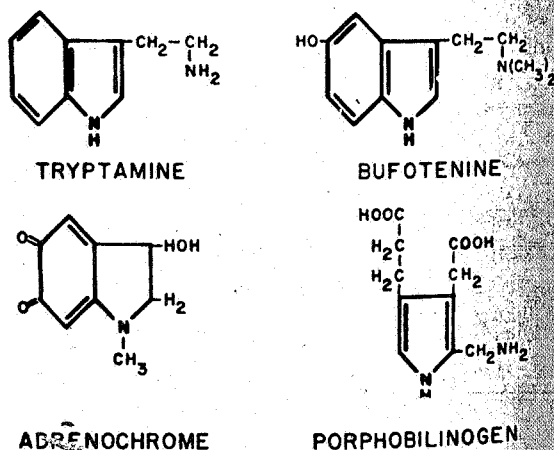


Figure 2

This "pink adrenaline" is adrenochrome, an oxidation product which is an indole in structure (Fig. 2). Osmond, Hoffer and Smythies, working in Saskatchewan, Canada, found a few years ago, that when this substance is injected intravenously, a schizophrenia-like model psychosis of as much as four days' duration might result. It has been difficult to repeat this work because adrenochrome is a very unstable compound, but their accounts are striking. More recently, Hoffer, one of the members of the Saskatche-

wan group, found that another adrenaline oxidation product, adrenolutin, also an indole, is capable of producing schizophreniform symptoms in man temporarily.

The "indole theory" is attractive, but is certainly not more than a possibility. Other compounds which are not indoles can produce symptoms suggestive of schizophrenia. Cannabis is one, as are the opiates and the bromides, among others. Perhaps a common denominator will be found in all these things, so that the chemical lesion in all schizophrenia-like model psychoses will emerge.

Two weeks ago at the annual meeting of the American Psychiatric Association in Chicago a preliminary report was made on another agent which mimics schizophrenia. Dr. Robert Heath, Professor of Psychiatry and Neurology at Tulane University, gave an account of withdrawing 500 cc. of blood from the the vein of a schizophrenic patient, of extracting it (the details have not yet been reported) and of injecting the extract in small quantities into monkeys and into man. I saw movies of two of Heath's subjects, volunteers from the convict population at a Louisiana prison. One became catatonic and mute, the other became paranoid, suspicious and profane. The effect lasted almost three hours. The changes were dramatic and striking. Heath believes that the toxic substance is a complex protein rather than an indole. It is too early to draw conclusions from this preliminary work, as Heath and his associates are the first to acknowledge, but it is a definite straw in the wind. This is the first time that a substance from a schizophrenic patient has made a normal person temporarily schizophrenic.

Hoffmann's serendipity, when he accidentally swallowed LSD-25, has had far-reaching effects in a short time, and one senses that this impetus to investigation of the biochemistry of schizophrenia may lead us out of the wilderness of doubt and speculation into a knowledge of the etiology of the disease. We may hope that the answer to this riddle is not too far away, but it would be useless and irresponsible to hazard a guess about the length of time it may take, or what the final answer might be. It will be interesting to sit by and see where this work all leads. If an answer comes forth, definitive therapy, better than the tranquilizing or ataractic drugs now available, cannot be far away.

SUMMARY

The accidental swallowing of a minute quantity of lysergic acid diethylamide (LSD-25) by a research worker a decade ago has touched off a widespread inquiry into compounds which temporarily mimic schizophrenia when they are ingested, snuffed or injected. A search through anthropologic lore discloses that many, but not all, of these substances belong to the chemical family of indoles. It is felt that investigation of these "model psychoses" of schizophrenic type may well lead toward a fuller understanding of the biochemical "lesion" in the clinical disease, and may put us on the track toward a rational therapy based on etiology rather than on empiricism.

Current Comment

From the Sioux City Journal—

The Newcastle community honored Dr. and Mrs. R. C. Richards at an open house in October in commemoration of the doctor's 45 years of service to the community. Dr. Richards and his family came to Newcastle in 1911.

His life here has been typical of that of a country doctor, battling the elements to care for the sick and sharing the joys and sorrows of the community. He was interested in obstetrics and officiated at 1,747 births. The first child was brought into the world on May 21, 1911, and the last one on September 15, 1955. Since that time he has discontinued this type of practice.

Dr. Richards purchased one of the early-day Buicks and had it shipped to this community but because of the condition of the roads in this area he still made most of his calls by horse and buggy.

The doctor still conducts a general practice here despite his 79 years. He loves outdoor exercise, especially hunting and fishing. He also raises his own vegetables and fruit and during the winter cuts wood with an ax for exercise. He attributes his good health throughout the years to his outdoors activities.

He entered medical college at the University of Michigan and completed his medical studies at Northwestern University in 1905.

The doctor began practice at Hopedale, Illinois, and practiced there five years before coming to Newcastle, making him a 50-year veteran of the profession.